Ray Peat's Newsletter

"On waxen tablets you cannot write anything new until you rub out the old. With the mind it is not so; there you cannot rub out the old until you have written the new." Frances Bacon

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Protecting and restoring nerves

In the 1950s, the food and drug industries were promoting polyunsaturated "essential" fatty acids as protectors against heart disease, because they lowered cholesterol. Estrogen was being promoted as the cure for infertility, menopause, and numerous other problems, and the fact that it lowered cholesterol was seen as another marketing opportunity. The development of new diuretics to treat high blood pressure led to the demonizing of salt, and new drugs to treat diabetes led to indoctrinating the public with the idea that sugar was harmful.

For the television audience, these things became part of "mainstream medical science," and they are still influential ideas, visible in medical journals, affecting the ways physiological events are interpreted. To understand any problem, such as malfunction of nerves, all of these stereotypes have to be reconsidered--the ways sugars, fats, cholesterol and hormones interact are involved in the normal and abnormal functions of any kind of cell.

For example, there is still a general neglect of the difference between cholesterol itself, and cholesterol that has been altered by the attachment of a fatty acid. These are two distinct molecules, with extremely different functions in cells. (I'll refer to these as free cholesterol and the ester form of cholesterol.) In a newborn child, the large amount of cholesterol in the brain is almost entirely the simple free molecule, which has been synthesized from sugar during gestation, while in the senile Alzheimer's disease brain, cholesterol is mostly in the ester form, attached to a fatty acid. This kind of change in balance occurs in other failing tissues, and is affected by the diet and by environmental stresses.

The incidence of "diabetes" has been increasing rapidly in most parts of the world. The original understanding of diabetes was that it was a wasting disease, involving excessive urination and the loss of a lot of glucose in the urine, with most of the glucose derived from the breakdown of the body's protein. It involved a deficiency of insulin, and came to be treated by regular injections of insulin. Later, it was discovered that many obese people had very high blood glucose, and also had a normal amount of insulin. The first, somewhat rare condition, was named "type I, insulin dependent" diabetes, the second, more common condition, was named "type II, insulin resistant" diabetes. Both of these conditions have been increasing rapidly around the world.

Despite the ability to regulate blood sugar with insulin, about half of the people who have been diagnosed as "diabetic" will develop problems with the degeneration of nerves, including autonomic nerves that regulate the circulatory and digestive systems and other functions, the motor nerves that control movement, the sensory nerves, especially for the hands and feet, and the optic nerves and retinas.

The carpal tunnel syndrome, in which the fingers become numb or develop a tingling or burning sensation (resulting from compression caused by swollen connective tissue in the wrist), is fairly common in the general population, including people who experience hypoglycemia, but it's sometimes an early symptom of diabetes. People diagnosed as diabetic are about 40% more likely to experience it. This syndrome is about three times more common in women than in men. Usually, the carpal tunnel syndrome disappears quickly when hypothyroidism is corrected.

Nerve malfunctions clearly caused by hypothyroidism overlap with the degenerative neuropathies of diabetes. If a person with diabetes is unable to oxidize glucose (and instead, wastes it), the liver's stores of glycogen are depleted, and the ability to activate thyroxin by deiodination, forming T3, will be decreased. Deficiency of the active T3 hormone decreases the ability to oxidize glucose and to store glycogen, in a vicious circle. The medical habit of thinking in terms of discrete diseases has caused many physiological principles to be overlooked.

Because an obvious swelling and constriction of the connective tissue in the carpal tunnel is the immediate cause of the nerve malfunction, carpal tunnel syndrome isn't usually considered as one of the diabetic neuropathies. The medical profession is committed to the idea that the essence of diabetes is the presence of high blood sugar, and that the cause of the nervous degeneration must be found in the hyperglycemia.

Another condition that isn't usually included in the "diabetic neuropathies" is optic neuritis. Although optic neuritis, which can cause sudden loss of vision, and affects mostly young people, especially women, is considered to be an autoimmune inflammatory problem, it's often associated with the development of diagnosed diabetes. (Warren and Warren, 1983.)

The distinction between diabetic neuropathy and other nerve problems is hindering the understanding of diabetes itself, as well as helping to mystify the nature of nerve function and malfunction.

There is a narrow and well defined medical orthodoxy on the subject of diabetic neuropathy. The nerve malfunctions are explained primarily in terms of (1) microvascular disease, (2) glycation of proteins by sugars and their oxidation products, (3) the activation of protein kinase C (PKC), (4) activation of the polyol or sorbitol pathway leading to cell swelling and depletion of NADPH and NAD+, with reduction of nitric oxide and glutathione and loss of protection against oxidative damage, and, more recently (5) endoplasmic reticulum stress and (6) the unfolded protein response.

The problem with these hypotheses is that each of the processes can be more easily explained in terms of biological stress with an excess of free fatty acids, than in terms of excess glucose. Increased glucose is associated with the changes occurring in stress, because the hormones that respond to stress, adrenaline and cortisol, increase glucose. To distinguish causes and effects it's necessary to look beyond mere associations.

For example, the diabetogenic action of excessive growth hormone, which increases free fatty acids, involves the production of abnormalities in blood vessels (Rymaszewski, et al., 1991), inflammation (Liu, et al., 2002), and it is an activator of PKC (Nivet, et al, 1993). Growth hormone increases free fatty acids and VEGF, and fatty acids and VEGF activate aldose reductase in the polyol pathway. (Growth hormone is secreted in response to hypoglycemia, providing fatty acids as an alternative source of energy.)

Most of these processes, especially 5 and 6, are reactions that protect against stress. They are increased by the stress of glucose deprivation (Zhang and Kauffman, 2006; Shinohara, et al., 2006), and are adaptive neuroprotective reactions (Yan, et al., 2014; Matus, et al., 2008) rather than being agents of neurodegeneration.

In the medical mechanisms of diabetic neuropathy, excess glucose is the cause, but the reason for its excess is essentially unexplained: It is either because of a lack of insulin, or because of an inability to respond to insulin. The lack of insulin is typically explained by "glucotoxicity" which kills the pancreatic beta cells, and the insensitivity to insulin is typically explained by an excess of sugar in the diet. This complex of hypothetical "explanations" is kind of a landmark in science, representing as much useless work as the Ptolemaic epicycles did 1000 years ago.

Simply getting outside the world of compartmentalized diseases, there is an abundance of evidence showing the variety of ways in which cells can fail. Energy is needed for cell maintenance and adaptation, and the type of fuel used to provide the energy is crucial. Fatty acids interfere with the oxidation of glucose, and this effect can be seen in heart failure, immunodeficiency, and

dementia, as well as in simple stress, diabetes, and many other situations (dementia: Montine and Morrow, 2005. Yaqoob, et al 1994.)

This competition between fatty acids and glucose, which has been called the "Randle cycle" for about 50 years, can be applied to the treatment of diabetes and other degenerative/stress problems by adjusting the diet, or by using supplements such as niacinamide and aspirin, which improve glucose oxidation by lowering the free fatty acids in the serum.

Stress, even emotional stress, decreases the barrier function of the intestine, allowing bacterial endotoxin to be absorbed. Endotoxin activates a variety of enzymes, including those that liberate free fatty acids from the tissues. This is associated with systemic inflammation, and conditions including liver cirrhosis, Parkinson's disease, and nerve inflammation (Garate, et al, 2013). This immediate direct effect of endotoxin, the lipolytic increase of free fatty acids in the circulation, blocks insulin-stimulated glucose uptake (Buhl, et al., 2013; Wellhoener 2011). Despite this now well established role of stress and endotoxin in the production of hyperglycemia, the medical diagnosis of "diabetes" is universally made without measuring either cortisol or endotoxin.

Increased serum lactate, which is a feature of diabetes, occurs quickly after the exposure to endotoxin, even in the presence of adequate oxygen ("aerobic glycolysis"), showing that the oxidative apparatus of the cell has been impaired (Bundgaard, et al., 2003). Several factors are involved in this effect on the mitochondria. Besides the direct effects of endotoxin and fatty acids, endotoxin's activation of the synthesis of prostaglandins and nitric oxide contribute to the metabolic shift toward inflammation and away from efficient oxidation of glucose.

The importance of free fatty acids in the development of diabetes has been simply demonstrated in the experiment of Wright and Lacy (1988) in which either endotoxin or fasting (both of which increase free fatty acids) increased the speed of onset and the intensity of the diabetes stimulated by low doses of streptozocin, destroying beta cells. The so-called "essential fatty acids" seem to be essential for that toxin to produce diabetes (Wright, et al., 1988; Wright, et al., 1995).

The glycation of proteins, which is increased in diabetes, is produced by various reactive substances, including methylglyoxal.

It has been traditional to think of glucose-derived lactic acid as the source of methylglyoxal, because some of it can be produced by the enzymic modification of glucose. However, in stress, when fat is being released into the blood stream, glycerol is also liberated from the stored fat. Serum glycerol is increased in diabetics, as in other lipolytic states, and it stimulates the synthesis of glucose. D-lactate, which is formed from methylglyoxal, is also increased in the serum of diabetics. In the lipolytic states, glycerol, rather than glucose, is a major source of this highly reactive material (Kondoh, et al., 1994).

The enzyme aldose reductase, which controls the polyol pathway, reacts more readily with methylgyoxal, detoxifying it, than it does with glucose. Its activity is greatly increased by the presence of methylglyoxal. It also detoxifies other reactive fragments produced by fatty acid breakdown during stress, protecting against protein carbonylation. In the lens, this enzyme protects against cataracts (Pladzyk, et al., 2006), suggesting that the medical inhibition of it would have harmful effects. By its effect on the peroxisome system (PPAR; Qiu, et al., 2008) it affects the balance (Beyer, et al., 2008) between the useful free form of cholesterol, precursor to protective steroids, and the ester form, which is associated with degenerative diseases including atherosclerosis and dementia.

When free fatty acids are increased by stress, they amplify other inflammatory signals, by being converted to prostaglandins. One of the actions of prolonged prostaglandin formation is the activation of aromatase, the enzyme that forms estrogen, at the expense of testosterone. In normal aging, most tissues, including fat, begin to produce some estrogen, but in diabetes its levels are increased. In experimental animals, 3 months of diabetes produced by streptozotocin increases aromatase in sciatic nerves and in the hippocampus (Burul-Bozkurt, et al., 2010). In the kidney, the diabetic increase in aromatase is associated with decreased

function; aromatase increases in the eye and other tissues (Prabhu, et al., 2010). Blocking aromatase and supplementing DHT, the form of testosterone that can't be converted to estrogen, reduces kidney injury in diabetic rats (Manigrasso, et al., 2012).

The increase of estrogen synthesis in many tissues such as fat cells and blood vessels, in itself promotes the changes associated with type 2 diabetes, including abdominal obesity, vascular malfunction, and loss of muscle (Williams, 2010, 2012; Baghaei, et al., 2003). In brain injury, astrocytes, the supportive glial cells that normally don't produce estrogen, begin producing estrogen and multiplying.

Depriving the brain of glucose (Estrada, et al., 2009) or oxygen stimulates the proliferation of astrocytes. In age-related dementia, there is an increase in astrocytes, and astrocytosis is a characteristic of the diabetic brain. The prion diseases, the "spongiform encephalopathies," involve an extreme overgrowth of the astrocytes.

In peripheral nerves, large nerve cells are associated with Schwann cells that synthesize pregnenolone, progesterone, and other steroids, and with satellite glia, that react to injury with some of the features of astrocytes, producing increased sensitivity of the nerves; in chronic injury, these satellite glia can activate the production of estrogen in the nerves (Schaeffer, et al., 2010), while their deterioration results in a reduced production of progesterone and its metabolites. Similar processes exist in the brain as well as in peripheral nerves.

A source of brain injury that is often neglected is bacterial endotoxin, and the nitric oxide and prostaglandin that it produces (Sheng., et al., 2011), especially when insulin is deficient (Li, et al., 2013). Continued exposure to endotoxin produces astrogliosis in animals (Wang, et al., 2010). The oligodendrocytes, which produce progesterone in the brain, are killed by the glial cells activated by endotoxin, and their replacement from stem cells is blocked (Pang, et al., 2009). Similar processes can occur in the peripheral nerves.

In good health, the formation of estrogen in nerve cells in response to moderate stress would stimulate the glial cells to produce more progesterone, to conteract the stress; progesterone, besides counteracting the stress, normally turns off estrogen production by inactivating the aromatase enzyme (Yilmaz, et al., 2011; Schmidt, et al., 1998).

Aldosterone is involved in many inflammatory and degenerative, fibrotic processes, including heart failure and kidney failure, by promoting production of nitric oxide and prostaglandins, and it can cause nerve damage by its actions on astrocytes (Min, et al., 2011). Estrogen stimulates the production of aldosterone (Kau, et al., 1999; Bekker and Svechnikova, 1981). Progesterone antagonizes both aldosterone and estrogen.

Cells synthesize steroids from the free form of cholesterol, and it is this form of cholesterol which is depleted in the Alzheimer's disease brain, and in atherosclerotic plaques, while the cholesterol esters are increased (Boettcher, et al., 1964; Ando, et al., 1984; Wallin, et al., 1989; Roher, et al., 2002). The ester form is required for the proliferation of at least some cancers. Cholesterol in the free form protects brain cells against cytotoxins (Sponne, et al., 2004). Things that inhibit cholesterol synthesis in the brain cause neurodegeneration (Ledesma and Dotti, 2005; Abad-Rodriguez, et al., 2004). The formation of myelin is associated with formation of the free form of cholesterol (Ghosh and Grogan, 1990.)

Besides the failure to synthesize enough cholesterol, the loss of free cholesterol by its combination with fatty acids is recognized in the neurodegenerative diseases and in autism (Anchisi, et al., 2012). The oral supplementation of purified cholesterol has been used to treat autism (Bukelis, 2007).

There is evidence that estrogen inhibits the liberation of cholesterol from the ester form, and that progesterone increases the activity of the enzyme that removes the fatty acid (Gandarias, et al., 1984; Peiretti, et al., 2007; Mulas, et al., 2011). Hypothyroidism, which increases the ratio of estrogen to progesterone, reduces the synthesis of cholesterol. Thyroid hormone activity corresponds to a shift of cholesterol toward the free form (Field, et al., 1986; Severson, et al., 1984; Severson and Fletcher, 1981), which would be expected, since thyroid hormone increases the

production of pregnenolone and progesterone from cholesterol. Since the 1980s, the multiple dangers of low cholesterol have been documented, but the cholesterol-lowering industry has diligently obscured the evidence.

By the 1970s, there was clear evidence of progesterone's brain-protective effects, and of the neurotoxic effects of unopposed estrogen, mostly from animal studies. A few people were using progesterone supplements to treat neurological diseases. It was known that the brain's concentration of progesterone and DHEA was much higher than their concentration in the blood, but it was only in the 1980s that it was shown that they are synthesized in the brain, and a few years later, they were shown to be synthesized in the peripheral nerves. The concentration of these neurosteroids decreases with age, but diabetes causes an exaggerated and premature decrease of them in the brain and peripheral nerves (Caruso, et al., 2008; Pesaresi, et al., 2010).

Stimulating their increase with a synthetic drug (Cermenati, et al., 2010), or directly supplementing progesterone is protective against the neuropathic effects of diabetes (Leonelli, et al., 2007; Roglio, et al., 2008; Sameni, et al., 2008).

The effects of progesterone on nerve cells are comprehensive. In the developing brain, it controls the availability of intracellular cholesterol for synthesizing neurosteroids, and regulates the provision of sugar which is required by mitochondria for the energy needed to synthesize the steroids, and in mature cells it regulates the two-way flow of substance in the axons, which transports cholesterol, mitochondria, proteins, and other substances from the distant cell bodies. It stabilizes the metabolic apparatus of the mitochondria, and inhibits the production of nitric oxide by mitochondria, which in the absence of progesterone would block the use of oxygen. In myelin-forming cells, it has multiple functions, maintaining or restoring their ability to produce myelin, and their ability to provide steroids to the axons they surround. It reduces the inflammatory substances that would make the nerves overexcitable, and it accelerates the transmission of nerve impulses, which is slowed in diabetes. It inhibits the release of fatty acids, reducing inflammation and protecting against their multiple harmful effects.

The drug industry recognizes its tremendous importance, and they are looking for synthetic chemicals that will increase its production in the brain and peripheral nerves without the serious side effects the present stimulants have, such as the SSRI antidepressants, and the industry is also interested in metabolites of progesterone, such as allopregnanolone, which is therapeutic for dementia, but which (being near the end of a metabolic sequence) might not have the radically restorative functions of progesterone, making it a better product for their business.

Cholesterol and the neurosteroids have a protective role in conditions that have been considered to be very different: Amyotrophic lateral sclerosis, epilepsy, Alzheimer's disease, schizophrenia, autism, diabetic neuropathy, depression, mania, hyperactivity, multiple sclerosis, for example.

Many simple therapies and foods synergize with progesterone--aspirin, caffeine, niacinamide, sugar, thyroid, pregnenolone, vitamins D, E, and K, stress reduction. Regular exposure to bright light, and avoiding hypothermia, are important.

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